IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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|---|---|---|
| In re application of | : | **Confirmation No. 2307** |
| Monique BERWAER et al. | : | Attorney Docket No. 2004_0980A |
| Serial No. 10/500,454 | : | Group Art Unit 1615 |
| Filed February 8, 2005 | : | Examiner Eric E. Silverman |
| PHARMACEUTICAL FORMULATIONS WITH MODIFIED RELEASE | : | **Mail Stop: AMENDMENT** |

**DECLARATION UNDER 37 C.F.R. 1.132**

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Michel DELEERS the undersigned, a citizen of Belgium, residing at Square des Braves, 12 B-1630 LINKEBEEK, BELGIUM, do hereby declare:

1. That I am an inventor of the above-identified application.

2. That I graduated from Université Libre de Bruxelles, Belgium: Ph.D. in chemistry & Doctor in Sciences.

3. That I currently work at UCB Pharma.

4. That I have read the specification and claims of the above-identified application as well as the Replies filed November 30, 2005, February 2, 2006, June 16, 2006, July 20, 2006 and August 1, 2006. I have also read the Office Actions, including the most recent dated November 24, 2006, which includes the following 103(a) obviousness rejections:

(1) rejection of claims 1-5 (actually claims 3-5) and 7 under 35 U.S.C. § 103(a) as obvious over Sunshine et al. in view of Kreutner et al., and

(2) rejection of claim 6 under 35 U.S.C. § 103(a) as obvious over Sunshine et al. in view of Kreutner et al. and in further view of Guy et al.

5. That in order to show the unexpected result that ingestion of the claimed pharmaceutical composition before a meal or after a meal does not significantly alter either the bioavailability or maximum plasma concentration of the active principle, I have examined the data and specification. Furthermore, the data I have examined and attached to this Declaration for purposes of showing the claimed formulation has this unexpected property were generated in experiments under my control and direction. The particular conclusions I have reached are as follows.

Example 4 on page 20 of the specification discloses administration of immediate-release efletirizine before and after a meal. In this example, the $C_{max}$ (maximum plasma concentration of efletirizine, ng/ml) and AUC (bioavailability of efletirizine, ng.h/ml) of the principle were markedly affected by consumption of a meal prior to administration of immediate-release efletirizine. In particular, the $C_{max}$ was decreased by 42% in patients who ingested the pharmaceutical after a standardized fatty meal as compared to fasting patients. Furthermore, the AUC was also decreased in patients who consumed the pharmaceutical after a standardized fatty meal as compared to fasting patients.

The subject matter of claims 3, 4 and 6 as amended is directed towards a pharmaceutical composition consisting essentially of efletirizine that contains one fraction that allows immediate-release (IR) and a second fraction that allows prolonged-release (PR) of efletirizine. The subject matter of the claims is further limited to particular ratios and amounts of immediate release/prolonged release efletirizine as indicated by the equations and ranges given in the claims.

The data in Example 5 on pages 20-22 of the specification indicate that a composition of the claimed invention is resistant to alterations in $C_{max}$ and AUC caused by eating a standardized fatty meal before administration of the pharmaceutical. In particular, Table 13 on page 22 shows that neither the $C_{max}$ nor the AUC significantly changed in patients who ate a standardized fatty meal as compared to fasting patients. These results are surprising and unexpected especially since the AUC and $C_{max}$ of the immediate release composition shown in Example 4, and discussed above, were markedly affected by ingestion of a meal prior to ingestion of efletirizine.

Pages 20-22 of the specification, containing the data discussed above, are attached to this Declaration. Furthermore, Attachment B is attached to this Declaration. This

attachment illustrates the calculated pharmacokinetics of efletirizine tablets containing an immediate-release and prolonged-release portion. The darkly shaded portion of the table in Attachment B indicates the particular amounts of immediate-release and prolonged-release efletirizine calculated as necessary to obtain the desired AUC and $C_{max}$.

As an experienced researcher in the field of pharmacology, it is my belief and expert opinion that it is surprising and unexpected that the claimed combination of extended release and immediate release of efletirizine is highly resistant to changes in maximum plasma concentration and bioavailability of the principal caused by ingestion of the claimed pharmaceutical either before a meal or after a meal.

6. Thus, it is my position and expert opinion that the inventions of claims 3, 4 and 6 as amended, have unexpectedly superior properties in regards to resistance to decreases in maximum plasma concentration and bioavailability of the principal caused by ingestion of the claimed pharmaceutical either before a meal or after a meal.

Therefore, it is my belief and expert opinion that the claimed invention is not rendered obvious by Sunshine et al. in view of Kreutner et al. or rendered obvious by Sunshine et al. in view of Kreutner et al. and in further view of Guy et al. because the references do not teach or suggest the unexpected superior property of the claimed invention discussed above.

7. I further declare that all statements made herein of my own knowledge are true and all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application or any patent issuing thereon.

Date: 20. 02. 2007

Signature: _____

Name: Michel DELEERS

obtained for the IR/PR dosage of 10/25 mg, in particular using the PR formulation: D (table 8).

Example 4. Administration of 60 mg of IR efletirizine: influence of a meal

A gelatin capsule containing 60 mg of efletirizine was administered to 20 fasting patients and to 22 patients who had eaten a standardized fatty meal beforehand. The main pharmacokinetic parameters are given in table 11.

Table 11. Main pharmacokinetic parameters after administration of 60 mg of efletirizine while fasting or after a meal

| Parameters | Fasting | After a meal |
|---|---|---|
| $C_{max}$ (ng/ml) | 1474 | 855 |
| $t_{max}$ (h) | 0.77 | 3.03 |
| AUC (ng.h/ml) | 6354 | 5784 |

It can be noted that having a meal has a very marked influence: the $C_{max}$ is decreased by 42%. The bioavailability is also decreased.

Example 5. Administration of 10 mg of IR efletirizine together with a PR tablet containing a dose of 25 mg

In a crossover trial, 12 volunteers received 3 types of treatments:

- 10 mg of IR efletirizine in the form of a solution and one PR tablet of 25 mg of efletirizine (J) while fasting;
- 10 mg of IR efletirizine in the form of a solution and one PR tablet of 25 mg of efletirizine (J) after a standardized fatty meal;

- 15 mg of IR efletirizine in the form of a solution, taken twice with a 12-hour interval

The formula of the PR tablet containing 25 mg of active principle (J) used in this study is given in table 12. The first 3 components are granulated. The last 3 are then added and the mixture is compressed. The tablet J is a repeat of the composition of the tablet F, to which a granulating agent, Povidone K30™, has been added.

Table 12. Composition of the PR tablet containing a dose of 25 mg of efletirizine (J)

| Components | Tablet J mg/tablet |
|---|---|
| Efletirizine dihyrochloride | 25 |
| Dibasic calcium phosphate hydrate (Emcompress™) | 30 |
| Polyvinylpyrrolidone (Povidone K30™) | 1.7 |
| Hydroxypropylmethylcellulose (Methocel K 15MCR™) | 28.4 |
| Colloidal silica (Aerosil 200™) | 0.6 |
| Magnesium stearate | 0.8 |

The main kinetic parameters are given in table 13.

Table 13. Main pharmacokinetic parameters after administration of 10 mg of IR efletirizine and 25 mg of PR efletirizine while fasting and after a meal, in comparison with the administration of 2 times 15 mg of IR efletirizine, with a 12-hour interval

| | IR/PR 10/25 mg | | IR 15 mg × 2 |
|---|---|---|---|
| Parameter | Fasting | After a meal | |
| $C_{max}$ (1) (ng/ml) | 280 | 355 | 307 |
| $C_{max}$ (2) (ng/ml) | | | 305 |
| $t_{max}$ (1) (h) | 1.5 | 4 | 0.6 |
| $t_{max}$ (2) (h) | | | 12.6 |
| AUC (ng.h/ml) | 2680 | 3031 | 2801 |

Surprisingly, contrary to what had been observed in example 4, having a meal does not cause the $C_{max}$ to decrease and the bioavailability is not significantly modified.

Also surprisingly, despite the absence of basifying agent in the PR formulation, the in vivo absorption proves to be constant and therefore independent of the pH, contrary to what had been observed in vitro in the dissolution tests described in patent application PCT/BE98/00033. This pH-independence results in small inter-individual variations after administration of the IR/PR form, and the coefficients of variation on the AUC are respectively 23% and 17% while fasting and after a meal.

## Example 6. Simulation of the surface areas under the curve for combinations of IR and PR forms of efletirizine

Based on the pharmacokinetics obtained in example 5, simulations were performed for combinations at various concentrations of efletirizine in IR and PR forms. For

Estimation of the bioavailability (%) of a mix of both immediate and extended release of efletirizine

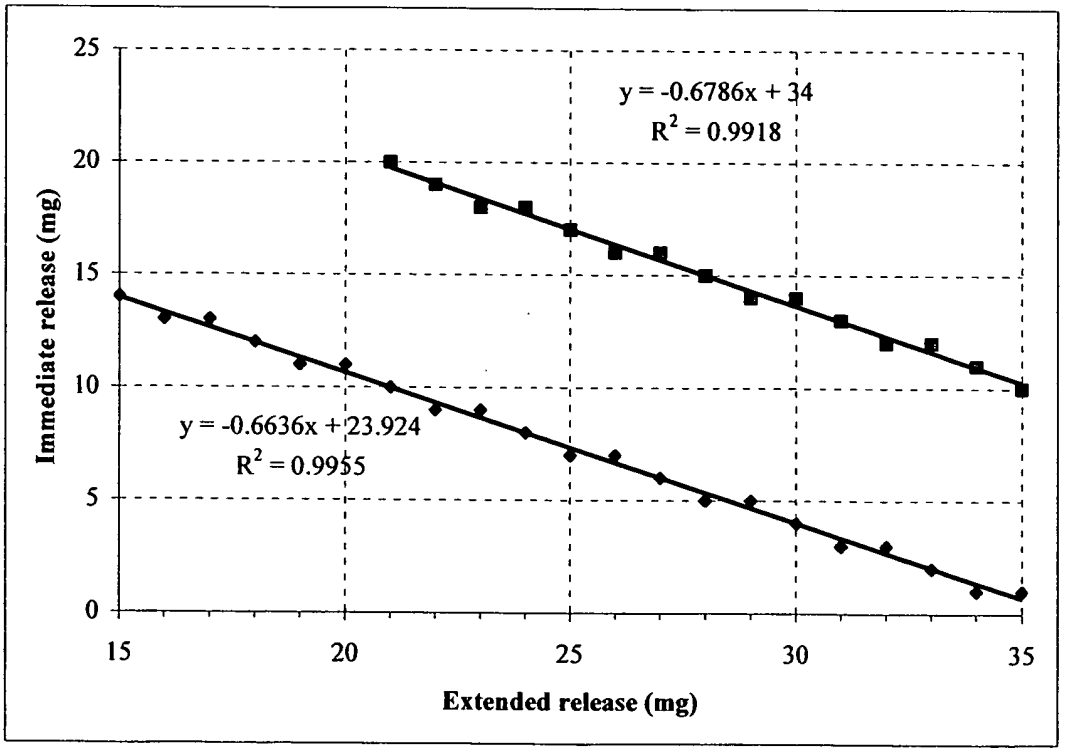
| Extended release (mg) | Immediate release (mg) | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 |
| 15 | 35.6 | 39.1 | 42.7 | 46.2 | 49.7 | 53.2 | 56.8 | 60.3 | 63.8 | 67.3 | 70.9 | 74.4 | 77.9 | 81.5 | 85.0 | | | | | | |
| 16 | 38.0 | 41.5 | 45.0 | 48.6 | 52.1 | 55.6 | 59.1 | 62.7 | 66.2 | 69.7 | 73.2 | 76.8 | 80.3 | 83.8 | | | | | | | |
| 17 | 40.4 | 43.9 | 47.4 | 50.9 | 54.5 | 58.0 | 61.5 | 65.0 | 68.6 | 72.1 | 75.6 | 79.1 | 82.7 | 86.2 | | | | | | | |
| 18 | 42.7 | 46.3 | 49.8 | 53.3 | 56.8 | 60.4 | 63.9 | 67.4 | 70.9 | 74.5 | 78.0 | 81.5 | 85.1 | | | | | | | | |
| 19 | 45.1 | 48.6 | 52.2 | 55.7 | 59.2 | 62.7 | 66.3 | 69.8 | 73.3 | 76.8 | 80.4 | 83.9 | | | | | | | | | |
| 20 | 47.5 | 51.0 | 54.5 | 58.1 | 61.6 | 65.1 | 68.6 | 72.2 | 75.7 | 79.2 | 82.7 | 86.3 | | | | | | | | | |
| 21 | 49.8 | 53.4 | 56.9 | 60.4 | 64.0 | 67.5 | 71.0 | 74.5 | 78.1 | 81.6 | 85.1 | | | | | | | | | | |
| 22 | 52.2 | 55.7 | 59.3 | 62.8 | 66.3 | 69.9 | 73.4 | 76.9 | 80.4 | 84.0 | | | | | | | | | | | |
| 23 | 54.6 | 58.1 | 61.6 | 65.2 | 68.7 | 72.2 | 75.8 | 79.3 | 82.8 | 86.3 | | | | | | | | | | | |
| 24 | 57.0 | 60.5 | 64.0 | 67.5 | 71.1 | 74.6 | 78.1 | 81.7 | 85.2 | | | | | | | | | | | | |
| 25 | 59.3 | 62.9 | 66.4 | 69.9 | 73.4 | 77.0 | 80.5 | 84.0 | | | | | | | | | | | | | |
| 26 | 61.7 | 65.2 | 68.8 | 72.3 | 75.8 | 79.3 | 82.9 | 86.4 | | | | | | | | | | | | | |
| 27 | 64.1 | 67.6 | 71.1 | 74.7 | 78.2 | 81.7 | 85.2 | | | | | | | | | | | | | | |
| 28 | 66.5 | 70.0 | 73.5 | 77.0 | 80.6 | 84.1 | | | | | | | | | | | | | | | |
| 29 | 68.8 | 72.4 | 75.9 | 79.4 | 82.9 | 86.5 | | | | | | | | | | | | | | | |
| 30 | 71.2 | 74.7 | 78.3 | 81.8 | 85.3 | | | | | | | | | | | | | | | | |
| 31 | 73.6 | 77.1 | 80.6 | 84.2 | | | | | | | | | | | | | | | | | |
| 32 | 76.0 | 79.5 | 83.0 | 86.5 | | | | | | | | | | | | | | | | | |
| 33 | 78.3 | 81.9 | 85.4 | | | | | | | | | | | | | | | | | | |
| 34 | 80.7 | 84.2 | | | | | | | | | | | | | | | | | | | |
| 35 | 83.1 | 86.6 | | | | | | | | | | | | | | | | | | | |

Lower 90% confidence limit on AUC(0-24)<80%

90% confidence limits of AUC(0-24) in the 80-125% range

90% confidence limits of both AUC(0-24) and Cmax in the 80-125% range

Upper 90% confidence limit on AUC(0-24)>125%






ATTACHMENT B